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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/357,704	07/20/1999	NEIL H. BANDER	242/024	9622

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	22

DATE MAILED: 01/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/357,704	BANDER, NEIL H.	
	Examin r	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-80,83-94 and 123-163* is/are pending in the application.

4a) Of the above claim(s) *160-163* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-80, 83-94, 123-159* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

The Amendment filed November 04, 2002 (Paper No. 19) in response to the Office Action of May 8, 2002 is acknowledged and has been entered.

Claims 81-82, and 95-122 were cancelled.

Claims 127-163 were added.

Claims 160-163 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 69-80, 83-94, 123-163 are pending and are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

Newly submitted claims 160-163 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 160-163 are drawn to antibody-directed therapies which necessarily include other therapeutic modalities such as hormone replacement with estrogen or an anti-androgen agents. These steps are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 160-163 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Rejections Maintained.

Claims 69-80, 83-94, 123-126 remain rejected, and new claims 123-159 are rejected under 35 USC 112, 1st paragraph, scope of enablement.

Applicants argue (Paper No. 19, page 20) that they have begun clinical trials using the antibodies of the invention and have demonstrated that the claimed antibodies against the extracellular domain of PSMA achieve not only effective targeting in vivo but also produce significant anti-tumor effects in both animal models and human subjects. Applicants point to the exhibits M-O. These arguments have been considered and are found persuasive- but only for treating prostate cancer; not for "preventing, or delaying development or progression of prostate cancer" for the reasons of record in Paper No. 17, pages 10-11.

Applicants argue (Paper No. 19, pages 21-22) that prostate cancer provides a particular opportunity for prevention and that the disease is often preceded by a long lag period between the precancerous condition and cancer. Applicants further argue that benign hyperplastic proliferation of the prostate can precede a cancerous state. Applicants argue that anti-PSMA antibodies could begin during the stage prior to cancer, to prevent or delay development or progression. These arguments have been considered but are not found persuasive for reasons of

record. Furthermore, reasonable guidance with respect to preventing any cancer (not just prostate cancer) depends upon quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer; not a mere proposal to begin using anti-PSMA antibodies in patients during the stage prior to cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

All other rejections are withdrawn in view of applicant's arguments and in view of the Inventor's declaration submitted under 37 CFR 1.131 in Paper No. 20.

New Rejections/Objections:

Election/Restrictions

Newly submitted claims 160-163 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 160-163 are drawn to antibody-directed therapies which necessarily include other therapeutic modalities such as hormone replacement with estrogen or an anti-androgen agents. These steps are materially

distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 160-163 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

Claim 139 is objected to for reciting "further comprises a cytotoxic drug" with regards to Claim 127 because Claim 127 already comprises a cytotoxic drug.

Claim Rejections - 35 USC § 112

Claims 140-152 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 140-152 recites the limitation "cytotoxic drug" in Claims 69, 83, 89 and 128. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 123, 128-131, 137-159 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth methods encompassing an antibody or antigen binding portion thereof which binds to the extracellular domain of prostate specific membrane antigen (PSMA), or monoclonal antibodies selected from the group consisting of an E99, a J415, a J533, and a J591 (see specification page 24). Thus, the written description is not commensurate in scope with the claims drawn to an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody (Claims 108 and dependents thereof). It is further noted that there is no support in the specification for the specific type of antibody referred to as IgG. Although an IgG antibody is well-known in the art, so are other types of antibodies, such as IgM, IgE, etc, and applicant's have not set forth clearly on the record any support for classifying these particular antibodies as IgG. The newly added claims have no clear support in the specification and the claims as originally filed. Hence, this is a new matter rejection. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP § 714.02 and § 2163.06 ("Applicant should specifically point out the support for any amendments made to the disclosure.")

Furthermore, it is noted that applicants argue (Paper No. 19, page 16) that the claimed antibodies are required to compete for binding with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591. Applicants argue that a skilled artisan "could use" art known methods together with the specific antibodies which have been made publicly available. Applicant's point to Example 10 in the specification that teaches a competition assay. However, example 10 on pages 38-39 is a competition study to determine whether E99, J415, J533, and J591 recognize the same or different antigenic sites- not whether other antibodies could be used to compete for recognition sites of these known antibodies. The results indicated that J591, J533, and E99 all compete for binding to the same antigenic site, whereas J415 recognized a different epitope. The specification only suggests that having pairs of non-competing antibodies (such as J591 and J415) would be useful for detecting "soluble" antigens. For example PSMA could be captured by J591 and detected by J415. Hence, the results do not provide evidence of or a written description for other antibodies (or antigen binding portions thereof) which compete for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims **69-71, 77-78, 126-127, 136-137, 139, 140, 141, 150-158** are rejected under 35 U.S.C. 102(e) as being anticipated by Israeli *et al.* (US Patent No. 5,538,866, October 1994).

Israeli *et al.* teach methods of imaging prostate cancer cells and methods for treating prostate cancer comprising administering polyclonal or monoclonal antibodies against PSMA in combination with a radioisotope, label, or cytotoxic agent (column 6, lines 53+; column 13, lines 5+, column 23) wherein said label is a biologically active enzyme (column 24, line 3) or ^{111}In (column 13, line 18). Examples of cytotoxic agents or conjugated drugs taught by Israeli *et al.* (column 23, line 49) include ricin (plant origin) and doxorubicin (bacterial origins) and pseudomonas exotoxin (biological protein). Although Israeli does not explicitly state that the antibodies bind to the extracellular domain of PSMA, Israeli teaches polyclonal and monoclonal antibodies directed to **specific portions** of the PSMA antigen (column 6, lines 48+; column 12, lines 64+). It is noted that the present specification does not specifically teach which regions of PSMA constitute the extracellular domain. Thus, absent evidence to the contrary, these portions appear to be portions of the extracellular domain. Furthermore, Israeli *et al.*, in general, teach antibodies which bind to PSMA, and include extensive structural information including the entire nucleic acid sequence of the antigen and the guidance necessary to create antibodies to **any** portion of the antigen. The patent further teaches that one of ordinary skill could select "specific regions" on PSMA to generate antibodies (column 12, lines 32+, column 23, lines 65+). This includes hydrophilic regions located on the "cell surface". To those of ordinary skill in the art, the cell surface is outside the cytoplasm and would comprise extracellular epitopes of PSMA. The patent further teaches, under antigenic site identification, (column 22), that the

knowledge of the cDNA for the antigen also provides for the identification of areas that would serve as good antigens for the development of antibodies for use against specific amino acid sequences of the antigen. Such sequences may be at different regions of the antigen such as "outside", membrane or inside of the PSM antigen. The patent further teaches (column 22, lines 40+), that the cDNA sequence implies that the antigen has the characteristics of a **membrane spanning protein**, with the majority of the protein on the exofacial surface. Thus, since it is clear that PSMA is a "membrane spanning protein", and since such proteins encompass intracellular, membrane spanning, and extracellular antigenic sites, the reference clearly anticipates antibodies to all regions or portions of the antigen- including those to the extracellular domain(s).

The patent further teaches that PSMA shares significant structural homology to the transferrin receptor (column 23, line 6), and that that transferrin receptors take up molecules into the cell by endocytosis, wherein the patent teaches that antibody-conjugated toxins specific for the transferrin receptor are toxic to tumor cells as tumor cells tend to express increased amounts of transferrin receptor (column 23, lines 35+). Thus, while the patent does not explicitly teach that the antibody-conjugates against PSMA will be internalized, the patent suggests that such antibody-conjugates will be internalized like those that bind to the transferrin receptor. Thus, inherently, such antibody-conjugates, as taught by Israeli, will be internalized. Further, although Israeli does not explicitly teach that the methods will treat a prostate metastasis, such as those involving bone marrow or a lymph node, inherently such antibody-conjugates would also treat a prostate metastasis as the antibodies of the invention would bind to the PSMA antigen on prostate cells irrespective of their location, and irrespective of their (prostate cells) viability.

Further, although the patent does not explicity teach the precise mechanisms of cell kill (i.e. those effective to initiate an endogenous host response such as complement mediated cellular cytotoxicity or antibody mediated cellular cytotoxicity), inherently, the administration of the antibodies as taught by Israeli *et al.* would initiate such host responses. Since the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the teachings of the prior art do not possess the same biochemical characteristics of the claimed methods, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 69-78, 123-127, 136-149, and 159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isreali *et al.* (US Patent No. 5,538,866, Oct. 1994) in view of Thomas *et al.* (Antibodies, A Practical Approach, Vol. 2, 1988) or Schlom, ("Molecular Foundations of Oncology", Chapter 6, pages 93-134, 1991).

Israel *et al.* teach as set forth above in the 102(e) rejection (Corresponding to claims 69-71, 77-78, 126-127, 136-137, 139-141, 150-158)

Isreali *et al.* does not include specific types of antibodies such as IgG and antibody fragments such as Fab, F(ab')2, or Fv, or specific (^{90}Y, ^{212}Bi, ^{213}Bi, ^{211}At, ^{186}Re, ^{131}I) and general (alpha, beta or gamma emitters) radioisotopic emitters conjugated to the antibodies, or modes of administration further comprising a pharmaceutically acceptable carrier, excipient, or stabilizer. (Corresponding to claims 72-76, 123-125, 138, 142-149, 159).

The specific imagining techniques, modes of administration, radiolabled-conjugates, and antibody fragments are well known in the art as set forth in applicant's disclosure of admitted prior art (pages 21-25). Also, Thomas *et al.* teach that antibodies can be used for in-vivo imaging, including an imaging device, antibody internalization, and radiation emitters including ^{131}I, ^{99}mTc, or ^{111}I. Thomas *et al.* further teach that radiolabeled sheep and goat IgG antibodies have been used predominately (page 226, and 230). Also, Schlom teaches that radiolabeled antibodies (page 108) can be used for in vivo imaging or treatment (i.e. ^{90}Y, page 109), including an imaging device (i.e., probes, page 103), intravenous and intracavity administration (i.e, page 101), antibody internalization, and radiation emitters such as ^{125}I, ^{131}I, ^{99}mTc, or ^{111}I. Schlom also teaches that antibody fragments such as Fab fragments are well known in the art (page 97).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the treatment methods taught in Israeli *et al.* (US Patent No. 5,538,866) so as to include the specific imagining techniques, modes of administration, antibody fragments, as well as the antibody IgG, and one would have been motivated to do so because these techniques are well-known in the art, include art-recognized equivalents and variations, wherein one of ordinary skill in the art would have a reasonable expectation of

success in implementing the modifications for the purposes associated with diagnostic and therapeutic applications.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
January 14, 2003

ANTHONY C. CAPUTA
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